REMARKS

The present application is directed to novel compositions and methods comprising therapeutic delivery compounds. The compounds are particularly suited for the effective delivery of genetic matter and other compounds to the interior of cells. Claims 1-4, 6-12, and 14-31 were pending prior to the issuance of the October 10, 2003, Office Action. Following entry of this amendment claims 1-4, 6-7, 9-12, 14-15 and 17-34 will be pending. Claims 1-3, 9-11, and 17-31 are amended and claims 8 and 16 are canceled. New Claims 32-34 have been added. No new matter is added and support for the amendments is found throughout the specification.

Claim objections

In the October 10, 2003, Office Action the Examiner objected to claims 1-4, 6-12 and 14-31 stating that the claims did not recite a molecular weight unit or define the subscripts "a" and "b". Applicants respectfully submit that the claims in questions have now been amended to disclose the molecular weight in Daltons. In addition, the claims have been amended to define the subscripts "a" and "b". Accordingly, Applicants respectfully submit they have overcome the Examiner's objection and request its withdrawal.

Claim rejections under 35 U.S.C. § 112, 2nd paragraph

In the October 10, 2003, Office Action the Examiner rejected claims 1-4, 6-12, and 14-31 under 35 U.S.C. 112, 2nd paragraph for failing to particularly point out and distinctly claim the subject matter. The Examiner stated that the intended scope of the nucleic acids intended to be embraced is unclear. Applicants respectfully traverse the rejection and assert that the amended claims define one or more nucleic acid molecules. Claim 1, 9, 24-25 and 32 recite a nucleic acid molecule selected from the group consisting of: "expression vectors which encode gene products, genes, oligonucleotides, antisense oligonucleotides, triplex DNA compounds, ribozymes, or a mixture thereof". Support for the incorporation of these terms can be found throughout the specification. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. 112, second paragraph.

The Examiner rejected claims 17, 20 and 28 as indefinite, stating that it is unclear whether the recited nucleic acid sequence is required to encode an antisense oligonucleotide, or whether antisense oligonucleotide is an alternative to nucleic acids. Applicants respectfully submit that the amended claims now clarify that one or more nucleic acids molecules is a gene or an antisense oligonucleotide. Applicants respectfully assert they have overcome the rejection under 35 U.S.C. 112, second paragraph and request its withdrawal.

Claim 31 has been amended to correct the lack of antecedent basis of "the animal".

Claim rejections under 35 U.S.C. § 102

In the October 10, 2003, Office Action the Examiner rejected claims 1-4, 8-12, 16-20 and 25-28 as anticipated by Allison et al., U.S. 5,376,369 (hereinafter "Allison et al.") under 35 U.S.C. 102(b). The Examiner stated that Allison et al. teach that "Pluronics L101, L121 and L122 could be used as an adjuvant in the delivery of whole viruses *in vivo* as vaccines. The limitation requiring an expression vector capable of expressing the genes is anticipated by the viruses themselves, which are capable of expressing their own genes".

Applicants respectfully traverse the rejection and submit that Allison et al. disclose the use of block polymers such as L101, L121, L122 and an immunopotentiating amount of a muramyldipeptide as an adjuvant in the delivery of whole viruses *in vivo* as vaccines (see abstract, line 1-5; Col 3, lines 49-61; Col 17, lines 38-41). The glycopeptide is considered by Allison et al., to be an **essential** feature of the invention. In contrast, the instant invention does not require a glycopeptide in addition to the block polymer and the one or more nucleic acid molecules. Therefore the prior art cannot be considered an anticipatory 102(b) reference because it does not teach all the claimed limitations.

In addition, the Examiner has based the 102(b) rejection on claims 1-4, 8-12, 16-20 and 25-28 which do not exclusively recite the use of an expression vector or whole virus. Although a whole virus is comprised of nucleic acid sequences, it is unclear how Allison et al., teach or disclose the use of block copolymer and a nucleic acid sequence that is not the entire viral genome (i.e. without other promoter/regulatory regions or other transcriptional factors), for example, the use of a small (<15 base pair) oligonucleotide, as disclosed in Example I of the current specification. Furthermore, even if Allison et al. disclosed a teaching

of one or more nucleic acid molecules in conjunction with the block copolymer, Allison et al. require as an essential element, the glycopeptide, which is omitted from the instant claims.

Applicants submit that nucleic acid molecules, such as oligonucleotides, antisense oligonucleotides, genes, expression vectors encoding viral genes are disclosed in the specification (see working Examples). In contrast, Allison et al. demonstrate that the use of whole viruses in combination with a polyoxyethylene-polyoxypropylene (POE-POP) copolymer and glycopeptide are capable of acting as a vaccine adjuvant. Applicants respectfully submit that the teachings of Allison et al. and the present application are patentably distinct, and cannot therefore be considered anticipatory. Accordingly, Applicants respectfully request the withdrawal of the rejection of claims 1-4, 8-12, 16-20 and 25-28 under 35 U.S.C. 102(b).

The Examiner also rejected claims 1-3, 8-11, 16-21 and 25-29 as being anticipated under 35 U.S.C. § 102(e) by Wasmoen et al., U.S. 5,656,275 (hereinafter "Wasmoen et al.") as evidenced by Osorio et al., WO 99/39733 (hereinafter "Osorio et al."). The Examiner stated that "Wasmoen et al. teach that Pluronic L121 could be used as an adjuvant in the delivery of whole viruses *in vivo* as vaccines". Wasmoen et al. exemplify a virus in which the antigen is expressed and incorporated into the viral particle prior to administration of the virus to the recipient animal. The Examiner also referenced Osorio et al., who disclose recombinant raccoon poxviruses, similar to those of Wasmoen et al., containing foreign genes encoding antigens and immunomodulatory factors for expression in the recipient.

Applicants respectfully traverse the Examiner's rejection. In order to teach the invention the patent must be explicit and detailed enough to permit or "enable" one with ordinary skill in the art to reproduce the invention without undue experimentation. Wasmoen et al. disclose that an acceptable adjuvant may be added to the whole virus, such as L121, but do not provide enablement of how L121 may be incorporated, or what effect L121 will have on the functionality of the composition. In contrast, Osorio et al. teach that it is not essential to provide an adjuvant, such as a block polymer, "one advantage of a recombinant raccoon poxvirus is that adjuvant and carriers are not required to produce an efficacious vaccine, and in some cases, the advantages of the poxvirus of the present inventions would be precluded by the use of some adjuvants" page 5, lines 25-28. This is in contrast to the present specification

where the use of the recited block polymers is required. Indeed, it is the individual properties of the block copolymers which alter the hydrophobicity and consequently the solubility of the composition, resulting in the unexpected increase in the viability of cells exposed to a transfecting agent (See Table IV).

Furthermore, the composition of Osorio et al. is dependent on the whole virus genome and also the "envelope and core in which the genome is packaged" page 6, lines 29-31. In both Osorio et al. and Wasmoen et al. it is not the viral nucleic acids *per se* that are required for vaccine activity but rather the protein antigens produced by the whole virus as a result of gene expression within the genome. In contrast, the present application describes the use of nucleic acid molecules including oligonucleotide sequences that may or may not possess antisense activity, that can be delivered across membranes wherein said nucleic acid molecules may modulate the action of specific genes within the host (as shown in the working examples of the specification). Finally, neither Wasmoen et al. nor Osorio et al. teach or suggest the addition of low molecular weight alcohol and Tween 80 to a composition comprising a non-ionic block copolymer and one or more nucleic acid molecules as instantly claimed. Applicants respectfully submit that the above references fail to teach or suggest all the claimed limitations. As such, Applicants believe they have overcome the rejection under 35 U.S.C. 102(e) and request its withdrawal.

The Examiner also cited Lee et al., stating that they describe a method of transfecting cells *in vitro* with plasmid DNA or antisense oligonucleotide in the presence of poloxamer, for example F68. The molecular weight of the hydrophobic portion (POP) of the poloxamer is 950-4,000 Daltons, and the hydrophillic (POE) portion of the block copolymer, constitutes 45-90% of the weight of the polymer. The F68 polymer comprises, more specifically, a POP molecular weight of 1750 and an 80% portion of POE.

Applicants respectfully traverse the rejection and state that the block polymer characteristics of F68 are in contrast to the high molecular weight polyoxypropylene (POP), and low percentage polyoxyethylene (POE) compositions described herein. Applicants respectfully submit that the amended claims fail to recite a polymer as described by Lee et al. having the following characteristics: a POP portion of the block polymer comprising a molecular weight of 950-4,000 Daltons, and a POE portion of the block copolymer,

constituting 45-90% of the total weight of the block polymer. Applicants respectfully submit that this rejection under 35 U.S.C. 102(e) is moot in view of the instant claims and request its withdrawal.

Claim rejections under 35 U.S.C. § 103 rejections

In the October 10, 2003, Office Action the Examiner rejected claims 1, 6, 7, 9, 14 and 15 under 35 U.S.C. 103(a) as being unpatentable over Wasmoen et al. in view of Miyamura et al., U.S. 5,656,275 (hereinafter "Miyamura et al."). The Examiner stated that Wasmoen et al. teach that "Pluronic L121 could be used as an adjuvant in the delivery of whole virus vaccines *in vivo*. Wasmoen et al. does not teach the addition of a surfactant and an alcohol to the vaccine. Miyamura et al. teach vaccines that are often modified by the addition of ethanol or Tween 80. Arriving at the appropriate concentrations of these additives is considered routine optimization". The Examiner concludes that the invention was *prima facie* obvious.

Applicants respectfully traverse the rejection. Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, *absent some teaching, suggestion or incentive supporting the combination. ACS Hospital systems, inc. v. Montefiore Hospital*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984). The mere fact that the reference **can** be combined or modified does not render the resultant combination obvious, unless the prior art **also** suggests the desirability of the combination. In re Kotzab, 217,F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000); *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990). MPEP §2143.01.

Miyamura et al. teach that excipients which are acceptable and compatible with the immunogenic ingredient may be added. Miyamura et al. fail to teach that Tween 80 alone is an effective additive. Miyamura et al. teach that MPL+TDM+CWS (bacterial extracts) in a 2% squalene/Tween 80 emulsion is an acceptable adjuvant. In addition, Miyamura et al. fail to teach or suggest the combination of excipients, ethanol and Tween 80 as claimed. This reference clearly requires the three bacterial components in conjunction with squalene and Tween 80 to be effective.

As described above, Wasmoen et al. does not teach or suggest the enablement of the block copolymer L121. In addition, Wasmoen et al. and Miyamura et al. teach vaccines that

require whole viruses (i.e. genomic and non-genomic material). Applicants respectfully submit that the claimed nucleic acid molecules are not taught or suggest by the cited references. The use of additives such as Tween 80 or ethanol are irrelevant with regard to obviousness, since the claimed invention as a whole is patentably distinct from Wasmoen et al. and Miyamura et al. Applicants respectfully submit they have overcome the rejection under 35 U.S.C. 103(a) and request its withdrawal.

Claims 25, 28 and 30 were rejected under 35 U.S.C. 103(a) as being unpatentable over Torrence et al., U.S. 5,583,032 (hereinafter "Torrence et al.") in view of Lee et al.

The Examiner stated that Torrence et al. teach a method of cleaving a viral RNA in cell culture by delivering to the cell antisense against the virus. Torrence et al. do not teach a composition comprising antisense and a non-ionic block copolymer. Lee et al. teach a method of transfecting cells *in vitro* with plasmid DNA or antisense oligonucleotide in the presence of poloxamer, for Example F68. The molecular weight of the hydrophobic portion (POP) of the poloxamer is 950-4,000 Daltons, and the hydrophilic (POE) portion of the block copolymer constitutes 45-90% of the weight of the polymer.

Applicants respectfully traverse the rejection. The F68 polymer has a POP portion of the block copolymer with a molecular weight of 1750 and an 80% portion of POE. This is in contrast to the high molecular weight POP and low percentage POE compositions claimed in the present application. As previously discussed, Applicants respectfully submit that the pending claims do not recite a polymer identical or similar to those described by Lee et al. having the following characteristics: POP portion of the block polymer comprising a molecular weight of 950-4,000 Daltons, and a POE portion of the block copolymer constituting 45-90% of the weight of the polymer. Applicants respectfully submit that neither Lee et al. nor Torrence et al. recite the block copolymers of the claimed invention, and cannot therefore be considered obvious over the present invention. Applicants respectfully submit that the rejection under 35 U.S.C. 103(a) is moot in view of the instant claims and request its withdrawal.

CONCLUSION

The foregoing is submitted as a full and complete Response to the Office Action mailed on October 10, 2003. For at least the reasons given above, Applicants respectfully submit that the pending claims are enabled, fully described, definite, novel and non-obvious. Accordingly, Applicants submit that the claims in the present application are in condition for allowance, and such action is courteously solicited.

A check for additional claims is enclosed. No additional fees are believed due; however, the Commissioner is hereby authorized to charge any deficiency, or credit any overpayment, to Deposit Account No. 11-0855.

The Examiner is invited and encouraged to contact the undersigned attorney of record at telephone number listed below, if such contact will facilitate an efficient examination and allowance of the application.

Respectfully submitted,

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